IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Patent Application of

von BORSTEL et al. Atty. Ref.: 1331-138

Serial No. 08/460,186 TC/A.U.: 1623

Filed: June 2, 1995 Examiner: Khare, Devesh

For: TREATMENT OF CHEMOTHERAPEUTIC AGENT AND ANTIVIRAL AGENT TOXICITY WITH ACYLATED PYRIMIDINE NUCLEOSIDES

* *

December 21, 2007

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

Appellant hereby appeals to the Board of Patent Appeals and Interferences from the last decision of the Examiner.

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(I) REAL PARTY IN INTEREST

The real party in interest is Wellstat Therapeutics Corporation, a corporation of the United States of America.

(II) RELATED APPEALS AND INTERFERENCES

The appellant, the undersigned, and the assignee are not aware of any related appeals, interferences, or judicial proceedings (past or present), which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

(III) STATUS OF CLAIMS

Claims 1-25 are pending and have been rejected. No claims have been substantively allowed. Claims 1-25 are the subject of the present appeal.

(IV) STATUS OF AMENDMENTS

No amendments have been filed since the date of the Final Rejection.

(V) SUMMARY OF CLAIMED SUBJECT MATTER

The invention as claimed in claim 1 relates to a method for preventing or treating toxicity due to a pyrimidine nucleoside analog by administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside (page 1, second complete paragraph; the paragraph bridging pages 10 and 11; page 20, second complete paragraph).

(VI) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The grounds of rejection to be reviewed on appeal are:

(A) The obviousness-type double patenting rejection of claims 1-25 as allegedly unpatentable over U.S. Patents 6,329,350; 5,246,708; 5,470,838; 5,583,117; 5,691,320; 6,020,320; 6,020,322; 6,060,459; 6,103,701; 6,232,298; 6,255,290; 6,274,563; 6,306,834; 6,316,426; 6,348,451; 6,403,565; 6,417,170; and 6,743,782; and

(B) The rejection of claims 1-25 under 35 U.S.C. §112, first paragraph, on lack of enablement grounds.

(VII) ARGUMENT

A. OBVIOUSNESS-TYPE DOUBLE PATENTING

At the outset, it is noted that the Action corrects the record in regard to the patents wrongly cited in the rejection. It is also noted that the rejection over U.S. patents 5,736,531, 5,968,914, 6,344,447, 6,258,795, 6,465,440, 6,472,378, 6,297,222, 6,054,441 and 5,770,582 has been withdrawn for the reasons stated on page 2 of the Action.

Claims 1-25 stand rejected on obviousness-type double patenting grounds as allegedly unpatentable over U.S. Patent No. 6,329,350 (the '350 patent), and applicant's other patents "of same scope" as follows: U.S. patents 5,246,708; 5,470,838; 5,583,117; 5,691,320; 6,020,320; 6,020,322; 6,060,459; 6,103,701; 6,232,298; 6,255,290; 6,274,563; 6,306,834; 6,316,426; 6,348,451; 6,403,565; 6,417,170; 6,743,782, by asserting that they all "have substantial overlap with the methods of the instant claims". Reversal of this rejection is respectfully requested.

The present application is a divisional of U.S. Application No. 08/176,485 (the '485 application), now U.S. Patent No. 5,736,531 (the '531 patent). The claims of the '485 application were restricted (June 28, 1994) among three inventions: Group I (drawn to methods for preventing or treating the toxicity caused by pyrimidine nucleosides), Group II (drawn to methods for treating cancer) and Group III (drawn to compositions of acylated pyrimidine nucleosides and a chemotherapeutic agent). The subject matter of Group I is being pursued in the present application. The subject matter of Group II is claimed in U.S. patent 5,968,914 and U.S. patent 6,344,447, and the subject matter of Group III is claimed in U.S. patent 5,736,531. The restriction requirement in the '485

application is evidence that methods for preventing or treating the toxicity caused pyrimidine nucleoside analogs are patentably distinct over: (1) methods for treating cancer; and (2) compositions. This evidence will be referred to below when considering the impropriety of the outstanding obviousness-type double patenting rejections.

Referring to the first complete paragraph on page 3 of the Action, the claims of the '350 patent are directed to methods for treating cancer. As seen from the restriction requirement in the '485 application (discussed above), methods for preventing or treating toxicity caused by pyrimidine nucleoside analogs are patentably distinct from methods for treating cancer. Accordingly, the claims of the subject application and the claims of the '350 patent are patentably distinct.

On page 4 of the Action, first complete paragraph, it is stated that it would be obvious to select a pyrimidine nucleoside in the issued patent for preventing or treating toxicity due to a pyrimidine analog because the composition containing an acylated derivative of a non-methylated pyrimidine nucleoside "would be considered an inherent property of a pyrimidine nucleosides for the treatment of cancer as well as preventing or treating toxicity due to a pyrimidine analog in an animal...." In response, as the USPTO has previously determined in the parent case that methods for preventing or treating toxicity caused by pyrimidine nucleoside analogs are patentably distinct from methods for treating cancer, it follows that the present claims are not rendered obvious by the claims of the '350 patent which are directed to cancer treatment.

On page 4 of the Action, it is further stated that there is substantial overlap of the claims of the present application with those of the '350 patent and the other cited patents

"because the method in the instant claims and the said patents are deemed same or substantial same and this obviousness-type double patenting rejection is necessary to prevent the unjustified or improper timewise extension of the 'right to exclude', granted by a patent and to prevent possible harassment by multiple assignees".

Applicant agrees with the position that, in the situation where double patenting exists, a rejection is proper to avoid possible harassment by multiple assignees. However, nowhere in the outstanding Action is there provided an explanation as to why double patenting exists as between the present claims and the claims of the cited patents. The Action simply makes the statement that there is "substantial overlap of the claims" because the method in the instant claims and the cited patents are "deemed same or substantial same." This conclusory statement is not a proper basis to reject the claims of the present case on obviousness-type double patenting grounds.

Referring to the second complete paragraph on page 3 of the Action, the claims of U.S. Patent No. 5,691,320 (the '320 patent) are directed to methods for treating or preventing tissue damage due to systemic inflammatory response syndrome, for treating or preventing sepsis, and for reducing the toxicity of a therapeutic cytokine or inflammatory stimulus. The claims of U.S. Patent No. 6,232,298 (the '298 patent) are directed to methods for treating cachexia. Thus, the claims of these two patents are not of the same scope as the '350 patent or the pending claims. As the claims of the '320 patent and the '298 patent are not directed to methods for treating cancer, the claims of the present application are not rendered obvious by the claims of either the '320 patent or the '298 patent.

The claims of U.S. Patent No. 5,583,117 are directed to methods of delivering exogenous uridine or cytidine to the tissue of an animal, of treating cardiac insufficiency, and of treating myocardial infarction. The claims of U.S. Patent No. 5,470,838 are directed to methods delivering exogenous uridine or cytidine to the tissue of an animal, of treating cardiac insufficiency, of treating cirrhosis of the liver, and of treating myocardial infarction. The claims of U.S. Patent No. 6,274,563 are directed to methods for treating diabetes and diabetic neuropathy. The claims of U.S. Patent No. 6,316,426 are directed to methods for treating a central nervous system disorder. Thus, the claims of these patents are not of the same scope as the '350 patent or the pending claims. Because the claims of the '117 patent, the '838 patent, the '563 patent and the '426 patent are not directed to methods for treating cancer, the claims of the present application are not rendered obvious by the claims of any of the '117 patent, the '838 patent, the '563 patent and the '426 patent.

The claims of U.S. Patent No. 6,403,565 are directed to various methods relating generally to protecting or treating the skin of a mammal, such as reducing mutation frequency in the skin of mammals that have been exposed to ultraviolet radiation or other mutagens. The claims of U.S. Patent No. 6,417,170 are directed to a method for inducing regression of inflammatory or hyperproliferative skin lesions. Examples of skin lesions treated by the method of the '170 patent include melanoma, basal cell carcinoma and squamous cell carcinoma (Claim 2). The claims of U.S. Patent No. 6,020,322 are directed to a method for cellular damage induced by radiation or other mutagens. The claims of U.S. Patent No. 6,103,701 are directed to a method of enhancing

hematopoiesis. The claims of U.S. Patent No. 6,306,834 are directed, *inter alia,* to methods of enhancing the delivery of exogenous 2'-deoxycytidine or 2'-deoxythymidine. The claims of U.S. Patent No. 6,348,451 are directed to a method for promoting wound healing. The claims of U.S. Patent No. 6,060,459 are directed to certain treatment methods utilizing oxypurine nucleoside compounds. The claims of U.S. Patent No. 6,020,320 are directed to methods of healing skin wounds, damaged liver tissue, or bone marrow. The claims of U.S. Patent No. 6,743,782 are directed to methods for enhancing the delivery of exogenous deoxyribonucleosides. The claims of U.S. Patent No. 6,255,290 are directed to a method for reducing the chance of developing skin cancer. The claims of U.S. Patent No. 5,246,708 are directed to a method of promoting wound healing. Since methods for preventing or treating the toxicity caused pyrimidine nucleoside analogs are patentably distinct over: (1) methods for treating cancer; and (2) compositions, the presently claimed invention is not rendered obvious by the claims of the above patents.

Reversal of the obviousness-type double patenting rejection is now believed to be in order. Such action is respectfully requested.

B. THE 35 U.S.C. §112, FIRST PARAGRAPH, REJECTION

Claims 1-25 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement, on the ground that the specification, while enabling effects of uridine and cytidine derivatives such as triacetyluridine (tau); octanoyl uridine; diacetyldeoxycytidine; and palmitoyldeoxycytidine (specification: Examples, pages 60-106), allegedly does not reasonably provide enablement for

preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside. The Action asserts that the selection of compounds of an acylated derivative of a non-methylated pyrimidine nucleoside is too broad based on the compounds disclosed in Examples, pages 60-106. The Action further asserts that, in the absence of data disclosing the effectiveness of an acylated derivative of a non-methylated pyrimidine nucleoside of claim 1 for preventing or treating toxicity in an animal, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Finally, the Action asserts that the absence of specific disclosures or the correlation of data to support applicant's assertions invites the skilled artisan to engage in undue experimentation. Reversal of this rejection is respectfully requested.

At the outset, is again noted that it is the USPTO, and not the Applicant, which bears the burden of establishing that an application does not satisfy the enablement requirement of 35 U.S.C. §112, first paragraph. As stated in In re Marzocchi:

> "As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367 (CCPA, 1971), (underlining added)

It is not sufficient for the USPTO to simply assert lack of enablement without also

providing support for its position. As further stated in In re Marzocchi:

> "In any event, it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." In re Marzocchi, 439 F.2d at 224, 169 USPQ at _ (internal citations omitted) (underlining added)

In the outstanding Action, the USPTO has not provided adequate "evidence or reasoning" in support of the enablement rejection. The Action states:

> "In the absence of....data disclosing the effectiveness of an acylated derivative of a non-methylated pyrimidine nucleoside of claim 1 for preventing or treating toxicity in an animal, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims." (June 21, 2006 Office Action, page 6).

It appears from the preceding quotation from the outstanding Action that the USPTO "doubts the truth or accuracy" of the present specification because Applicant has not presented "data disclosing the effectiveness of an acylated derivative of a non-methylated pyrimidine nucleoside of claim 1 for preventing or treating toxicity in an animal...". This is not sufficient reasoning to shift the burden to the applicant to address this ground of rejection. The Applicants have asserted that the disclosed compounds generally can be used in the claimed invention. Undue experimentation would not therefore be required to perform the invention as claimed. The USPTO improperly attempts to shift to the Applicants the burden of presenting evidence that the specification is enabling, contrary to the law under which the PTO bears the burden, in the first instance, of presenting evidence or reasoning in support of its doubts as to the truth of the

statements made in the disclosure. The rejection attempts to invoke unpredictability of the pharmaceutical art as a whole and to use that to try to shift the burden to the Applicants to prove that the invention does not work. As is clear from the case law citation above, this is not in accordance with the law.

A *prima facie* case of lack of enablement under Section 112, first paragraph, has not been established in this case. Reversal of the rejection is respectfully requested.

In conclusion it is believed that the application is in clear condition for allowance. Therefore, reversal of the Final Rejection and passage of the subject application to issue are earnestly solicited.

Respectfully submitted,

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(VIII) CLAIMS APPENDIX

1 (original). A method for preventing or treating toxicity due to a pyrimidine nucleoside analog comprising administering to an animal a pharmaceutically effective amount of an acylated derivative of a non-methylated pyrimidine nucleoside.

2 (original). A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acyl derivative of uridine, cytidine, deoxycytidine, or deoxyuridine.

3 (original). A method as in claim 1 wherein said toxicity is damage to hematopoietic tissue.

4 (original). A method as in claim 1 wherein said toxicity is damage to mucosal tissues.

5 (original). A method as in claim 1 wherein said pyrimidine nucleoside analog is an antineoplastic agent.

6 (original). A method as in claim 1 wherein said pyrimidine nucleoside analog is an antiviral agent.

7 (original). A method as in claim 1 wherein said pyrimidine nucleoside analog is an antimalarial agent.

8 (original). A method as in claim 1 wherein said pyrimidine nucleoside

analog is a cytotoxic analog of uridine.

9 (original). A method as in claim 1 wherein said pyrimidine nucleoside analog is a cytotoxic analog of cytidine.

10 (original). A method as in claim 1 wherein said pyrimidine nucleoside analog is an inhibitor of pyrimidine nucleotide biosynthesis.

11 (previously presented). A method as in claim 1 wherein said pyrimidine nucleoside analog is selected from the group consisting of 5-fluorouracil (5-FU), 5-FU prodrugs including Tegafur and 5'-deoxy-5-fluorouridine, 5-fluorouridine, 2'-deoxy-5-fluorouridine, prodrug derivatives of 5-fluorouridine or 2'-deoxy-5-fluorouridine, fluorocytosine, trifluoromethyl-2 '-deoxyuridine, arabinosyl cytosine, prodrugs of arabinosyl cytosine, cyclocytidine, 5-aza-2'-deoxycytidine, arabinosyl 5-azacytosine, 6-azacytidine, N-phosphonoacetyl-L-aspartic acid (PALA), pyrazofurin, 6-azauridine, azaribine, thymidine, and 3-deazauridine.

12 (original). A method as in claim 1 wherein said pyrimidine nucleoside analog is selected from the group consisting of AZT, dideoxycytidine, 5-ethyl-2'-deoxyuridine, 5-iodo-2 '-deoxyuridine, 5-bromo-2 '-deoxyuridine, 5- methylamino-2 '-deoxyuridine, arabinosyluracil, dideoxyuridine and (S)-1-(3-hydroxy-2-phosphonylmethoxypropyl) cytosine.

13 (original). A method as in claim 1 wherein said pyrimidine nucleoside

analog is 5-fluoroorotate.

14 (original). A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is triacetyluridine.

15 (original). A method as in claim 1 wherein said acyl derivative of a non-methylated pyrimidine nucleoside is ethoxycarbonyluridine.

16 (original). A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is triacetylcytidine.

17 (original). A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is diacetyldeoxycytidine.

18 (original). A method as in claim 1 wherein said acylated derivative of a non—methylated pyrimidine nucleoside is an acylated derivative of uridine, deoxyuridine, or cytidine, and said administering step also includes administering an inhibitor of uridine phosphorylase.

19 (original). A method as in claim 18 wherein said inhibitor of uridine phosphorylase is selected from the group consisting of benzylacyclouridine, benzyloxybenzylacyclo-uridine, aminomethyl-benzylacyclouridine, aminomethyl-

benzyloxybenzylacyclo-uridine, hydroxymethyl-benzylacyclouridine, and hydroxymethyl-benzyloxybenzylacyclouridine, 2,2'-anhydro-5-ethyluridine, 5-benzyl barbiturate, 5-benzyloxybenzyl barbiturate, 5-benzyloxybenzyl-1-[(1-hydroxy-2-ethoxy)methyl] barbiturate, 5-benzyloxybenzylacetyl-1-[(l-hydroxy-2-ethoxy)methyl] barbiturate, and 5-methoxybenzylacetylacyclobarbiturate.

20 (original). A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of cytidine or deoxycytidine, and said administering step also includes administering an inhibitor of cytidine deaminase.

21 (original). A method as in claim 20 wherein said inhibitor of cytidine deaminase is selected from the group consisting of tetrahydrouridine or tetrahydro-2'-deoxyuridine.

22 (original). A method as in claim 1 wherein said acylated derivative of a non-methylated pyrimidine nucleoside is an acylated derivative of uridine, cytidine or deoxycytidine, and said administering step also includes administering an inhibitor of nucleoside transport.

23 (original). A method as in claim 22 wherein said inhibitor of nucleoside transport is selected from the group consisting of dipyridamole, probenicid, lidoflazine or

nitrobenzylthioinosine.

24 (original). A method as in claim 1 wherein said administering step also includes administering an agent which enhances hematopoiesis.

25 (original). A method as in claim 1 wherein said administering step also includes administering a compound capable of enhancing the uptake and phosphorylation of nucleosides into cells.

(IX) EVIDENCE APPENDIX

None.

(X) RELATED PROCEEDINGS APPENDIX

None.